

EXTRAMURAL CLINICAL TRIAL APPENDIX C
EXCEPTIONS OR MODIFICATIONS TO THIS CRADA

Add the following new sections to the **Article 2. Definitions**:

- 2.12 **"Adverse Drug Experience"** means an adverse clinical experience as defined under 21 CFR §310.305 or §312.32 as applicable.
- 2.13 **"Annual Report"** means the brief report of the progress of an IND associated investigation which the IND sponsor is required to submit to the FDA within 60 days of the anniversary date that the IND went into effect (pursuant to 21 CFR § 312.33).
- 2.14 **"Clinical Data and Results"** means all information, data and results developed or obtained in connection with clinical trials sponsored by PHS and using Study Drug whether by intramural research scientists or Extramural Investigators.
- 2.14 **"Clinical Data and Results in PHS' Possession and Control"** means all data obtained by PHS under contracts with extramural contract investigators for completion of studies within the scope of the Protocol, and all information and data in the PHS sponsored IND for Agent.
- 2.15 **"Contract"** means a funding agreement that is a research and development contract that provides that the contractor perform for the benefit of the Government, with an expectation of completion of the stated research goals and the delivery of a report, data, materials or other product.
- 2.16 **"Extramural Investigator"** means the principal investigator who conducts research under a PHS-sponsored Grant or Contract.
- 2.18 **"FDA"** means the US. Food and Drug Administration.
- 2.19 **"Grant"** means a funding agreement that is an award of financial assistance, which may be provided for support of scientific research in a specific field of interest to the funding Federal agency.
- 2.19 **"IND"** means an Investigational New Drug Application submitted to the FDA to receive approval to conduct experimental clinical trials.
- 2.21 **"Protocol"** means the Protocol, including the Standard Operating Procedure (SOP) numbered _____, entitled _____, which is attached hereto as Appendix D and is made a part of this Agreement.
- 2.22 **"Steering Committee"** means the joint PHS/Collaborator research and development team whose composition and responsibilities with regard to the clinical experiments performed under this CRADA are detailed in the Protocol attached hereto as Appendix D.
- 2.23 **"Study"** means the work performed by the Principal Investigators and the Extramural Investigators in connection with the Protocol.

- 2.24 **"Study Drug"** means _____ [Fill-in name of agent, drug, or biological product] in a finished dosage form, for example, tablet, capsule, solution, etc., that contains _____ [Fill-in name of agent, drug, biological product] as the active agent generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an agent but is intended to be used as a placebo, as stated in the definition of "Drug product" at 21 CFR 21.0.3(a)(4).

Add a new **Article 3.3** as follows:

- 3.3 **Protocol Modification.** The Study shall be done in strict accordance with the Protocol and no changes in the finalized Protocol will be made unless mutually agreed upon in advance by both Parties. In the event that the appropriate Institutional Review Board (IRB) requires changes in the Protocol or the Informed Consent Form, both Parties agree to modify the Protocol and/or Informed Consent Form as appropriate.

Add a new **Article 3.4** as follows:

- 3.4 **Investigational New Drug Application.** The Parties expect that either PHS or Collaborator will submit an IND, which may cross-reference an IND, Drug Master File, or New Drug Application held by the other. In the event PHS elects to file its own IND, the Collaborator agrees to provide PHS background data and information and agrees to execute such documents as may be reasonably required to effect such cross-reference. The Collaborator's employees will be reasonably available to respond to inquiries from the FDA regarding information or data contained in the Collaborator's ND, Drug Master File, New Drug Application, or other information and data provided to PHS by the Collaborator pursuant to this Article 3.3. Nothing herein shall require the Collaborator to undertake additional studies of any kind or to prepare and submit any additional data to the FDA which are not already included in the Collaborator's IND, Drug Master File, or New Drug Applications. In the event that Collaborator supplies **CONFIDENTIAL** information directly to PHS in support of a PHS IND, such information will be protected in accordance with the corresponding Confidentiality provisions of Article 8 of this Agreement.

The Collaborator may sponsor its own clinical trials and hold its own IND for studies performed outside the scope of this CRADA from which all data is proprietary to the Collaborator for purposes of this CRADA.

Add a new **Article 3.5** as follows:

- 3.5 **Drug Information and Supply.** Collaborator agrees to provide PHS without charge clinical-grade Study Drug in sufficient quantity to complete the preclinical studies and clinical trial Protocol(s) sponsored by PHS. Furthermore, Collaborator agrees to provide without charge Study Drug, placebo, or unformulated analytical grade Study Drug or metabolites, if available, to PHS to supply Extramural Investigators for the development of mutually agreed upon analytical assays or ancillary correlative studies conducted in conjunction with PHS-sponsored protocols. Collaborator will provide Certificates of Analysis to PHS for each lot of finished product provided. For inquiries related to Study Drug, the contact person for PHS will be _____ [Name], _____ [Title], (Telephone Number (AC) (301) _____ - _____) and the Collaborator contact will be _____ [Name], _____ [Title], (Telephone Number (AC) (____) _____ - _____).

Add a new **Article 3.6** as follows:

- 3.6 **Drug Delivery and Usage.** Collaborator shall ship Study Drug to PHS in appropriately marked containers in accordance with 21 CFR §312.6. The PIs shall take reasonable steps to ensure appropriate record keeping and usage of Study Drug is maintained in accordance with the Protocol and any applicable laws and regulations relating thereto. Any unused quantity of Study Drug shall be returned to Collaborator by PHS at the conclusion of the Study or earlier termination subject to Article 10.6 of this Appendix C.

Add a new **Article 3.7** as follows:

- 3.7 **Protection of Human Subjects and Appropriate Care of Laboratory Animals.** All human clinical trials performed under this CRADA shall conform to the appropriate Federal laws, including, but not limited to all applicable FDA regulations and DHHS regulations relating to the protection of human subjects (*See* 45 CFR Part 46). PHS and Collaborator also agree to comply with all applicable Federal statutes and Public Health Service policies relating to the use and care of laboratory animals (see 7 USC Section 2131 *et seq.*). Additional information is available from the NIH Office for Protection from Research Risks, Telephone: (301) 496-7163.

Add a new **Article 3.8** as follows:

- 3.8 Monitoring. _____ shall be responsible for clinical site monitoring and the quality assurance of all data. Monitoring shall be done in compliance with FDA ***Good Clinical Practices Guidelines***.

Add the following to the end of **Article 4.1 Interim Reports**.

Steering Committee reports or copies of Annual Reports updating the progress of the CRADA research shall satisfy the reporting requirements under this Article 4.1. In addition, copies of the Annual Reports and other pertinent IND data (including, but not limited to, clinical brochure data, and formulation and preclinical data1 including toxicology findings) shall be exchanged by the Parties as they become available.

Add a new **Article 4.3** as follows:

- 4.3 **Adverse Drug Experience Reporting.** In accordance with FDA requirements, the Party which holds the IND shall establish and maintain records and make reports to the FDA as required by 21 CFR Sections 310.305 and 312.32, as applicable. In the conduct of research under this CRADA, the Parties also agree to adhere to specific NIH and _____[IC] guidelines and policies for reporting Adverse Drug Reporting, as specified in _____[Insert Protocol, SOP or document name which requires such reporting]. The Party which holds the IND agrees to provide the other Party copies of all Adverse Drug Experience reports concurrently with their submission to the FDA, including copies of any warning letters or other information affecting the safety and/or well-being of human subjects in research conducted under this CRADA.

Add a new **Article 4.4** as follows:

- 4.4 **Annual Reports.** The IND holder shall provide the other Party a copy of the Annual Report thirty (30) days prior to submission to the FDA. The reviewing Party will then have fourteen (14) days to review the Annual Report and to provide comments to the IND holder.

Delete Article 8.7 and in its place **add** the following:

- 8.7 **Publication.** The Parties are encouraged to make publicly available the results of their research. Before either Party submits a paper or abstract for publication or otherwise intends to publicly disclose information about a Subject Invention, Subject Data, Clinical Data and Results in PHS' Possession and Control, or Research Materials, the other Party shall be provided thirty (30) days to review the proposed publication or disclosure to ensure that Proprietary/Confidential Information is protected. The publication or other disclosure shall be delayed for up to thirty (30) additional days upon written request by any Party as necessary to preserve US or foreign patent or other IP rights.

Add a new **Article 8.8** as follows:

- 8.8 **Extramural Research and Data.** In pursuing the development of Study Drug pursuant to this CRADA, PHS may utilize Extramural Investigators for part or all of the completion of this Protocol through either Federal Grants or Federal contracts. However, said Extramural Investigators are not Parties to this CRADA, and this CRADA does not address rights to inventions made or data generated by Extramural Investigators. Nonetheless:
- a. Subject to the other provisions of Article 8 of this CRADA, PHS shall maintain, to the extent permitted by law, all Clinical Data and Results in PHS' Possession and Control as Proprietary and CONFIDENTIAL, and make them available exclusively to the Collaborator for its own use and for use in obtaining FDA approval for the commercial marketing of Subject Inventions and Study Drug products.
 - b. In the case of an Extramural Investigator being funded by Contract, PHS shall not execute a Contract for preclinical studies or clinical trials for the development of Study Drug unless the Extramural Investigator agrees to confidentiality provisions at least as restrictive as provided in this CRADA and to the Collaborator's use of data in accordance with Article 8.8 (a) for its own use and for use in obtaining FDA approval for the commercial marketing of Subject Inventions and Study Drug products.
 - b. In the case of an Extramural Investigator being funded by a Grant, PHS shall urge all Extramural Investigators participating in the Study sponsored by PHS and using Study Drug to cooperate exclusively with Collaborator in providing data for use in obtaining pharmaceutical regulatory approval for the commercial marketing of Study Drug. However, PHS' urging will not constitute a term or condition for making a grant award to said Extramural Investigators.
 - c. In seeking direct access to Clinical Data and Results or any other information that is in the possession of Extramural Investigators working with Study Drug under the sponsorship of PHS, Collaborator shall first contact the Project Officer, _____ [Name] of the _____ [Branch] at (AC) (____) ____ - _____ [Telephone]. Subsequent to authorization by _____ [Branch], Collaborator may directly contact the Extramural Investigators. Costs associated with providing Clinical Data and Results to Collaborator in customized formats shall be borne by Collaborator.

- d. Collaborator's exclusive access under subsection (a) above to Clinical Data and Results PHS' Possession and Control is dependent, however, upon Collaborator's continued development and commercialization of the technology. In the event that Collaborator discontinues development or commercialization of the technology without the transfer of its development efforts to another party within ninety (90) days of discontinuation, PHS retains the right to make the Clinical Data and Results in PHS' Possession and Control available to another party.

Add a new **Article 8.9** as follows:

8.9 Multi-Party Data and Intellectual Property Rights. For clinical protocol(s) where Agent is used in combination with another compound(s) which is (are) proprietary to an entity(ies) not a Party to this CRADA (hereinafter referred to as Second Party], the access and use of data derived from such combination studies, [hereinafter referred to as Multi-Party Data], by the Collaborator and Second Party shall be co-exclusive as follows:

- a. In situations where Agent is to be used in combination with another proprietary compound, PHS will provide all Parties with notice regarding the existence and nature of any agreements governing their use of Agent, including the design of the proposed combination protocol(s) and the existence of any obligations that might restrict PHS' participation in the proposed combination protocols.
- b. Collaborator agrees to permit use of the Multi-Party Data from these trials by the Second Party to the extent necessary to allow said Second Party to develop, obtain regulatory approval or commercialize its own proprietary compound. However, this provision will not apply unless said Second Party also agrees to Collaborator's reciprocal use of Multi-Party Data.
- c. Collaborator and Second Party must agree in writing prior to the commencement of the combination trials that each will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own proprietary compound(s).

Add the following sentence to the end of **Article 10.2 Unilateral Termination**.

Any Research Materials within Collaborator's possession which are a product of the Study must be transferred immediately to PHS before the desired termination date of the CRADA.

Add a new **Article 10.6** as follows:

10.6 Alternative Sources of Supply and Research License In the Event Collaborator Terminates Development of Agent

- a. In the event Collaborator elects to terminate its development of Study Drug without the transfer of its development efforts and obligations under this agreement to another party acceptable to PHS within ninety (90) days of discontinuation, and PHS wants to continue its development of Study Drug, then Collaborator will:

- (i) provide PHS with Study Drug and/or matching placebo from Collaborator inventory sufficient to complete the Study in the manner described in the Protocol. Or,
 - (ii) arrange, at Collaborator's expense, an independent contractor to manufacture and provide PHS Study Drug and/or matching placebo sufficient to complete the Study in the manner described in the Protocol.
- b. In the event that Collaborator is unable to meet the obligations imposed by (i) or (ii) above, at the discretion of PHS, Collaborator shall provide PHS all information and funding necessary to allow PHS to contract, manufacture, and purchase said Study Drug and/or matching placebo independent of Collaborator for use in preclinical studies and clinical trials. Such obligation shall last until either a date on which an alternate source of equivalent materials, acceptable to PHS, can be obtained by PHS, or two years after the date of notification by Collaborator to PHS that Collaborator elects to terminate its development of Study Drug, whichever comes first.
- c. Collaborator hereby grants to PHS a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any invention which Collaborator may have or obtain on Study Drug, its manufacture, or on the process for use of Study Drug, throughout the world, for medical research purposes. This license shall only become effective in the event Collaborator terminates its development of Study Drug without the transfer of its development efforts to another party within ninety (90) days of termination, and PHS elects to continue the development of Study Drug.

Modify the first sentence of **Article 12.3 Indemnification** as follows:

The Collaborator agrees to hold the US Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of the use by the Collaborator for any purpose of the Subject Data, Clinical Data and Results in PHS' Possession and Control, Research Materials and/or Subject Inventions produced in whole or part by PHS employees, under this CRADA, unless due to the negligence or willful misconduct of PHS employees.

Add a new **Article 13.13** as follows:

- 13.13 **FDA Meetings.** All meetings with FDA concerning clinical studies for the development of Agent within the scope of the CRADA Research Plan will be discussed by Collaborator and PHS in advance and will be held on mutually agreed upon dates. Collaborator reserves the right to set jointly with PHS the agenda for any such meeting.

Add a new **Article 13.14** as follows:

- 13.14 **Conflicts.** In the event of a conflict between the Protocol as attached hereto as Appendix D and the Model CRADA as modified by this Appendix C, the terms of the Model CRADA and this Appendix C shall prevail.

Add a new **Article 13.15** as follows:

13.15 **Statutory Compliance.** PHS and Collaborator agree to conduct the Study in accordance with the applicable portions of the Federal Food, Drug, and Cosmetic Act, 21 USC §301 *et seq.*, and its implementing regulations and other applicable Federal statutes and regulations.

Add the following to **Article 14.2 Survivability** as follows:

Articles 3.5, 4.3 and 10.6 and the last sentence of Article 10.2 as provisions that shall survive termination of this CRADA.